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MACROPHAGE MIGRATION INHIBITORY FACTOR LEVELS PREDICT NO-REFLOW IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

To elucidate whether Macrophage Migration Inhibitory Factor (MIF) levels anticipate no-reflow among ST-segment Elevation Myocardial Infarction (STEMI) patients. We enrolled 120 STEMI individuals given treatment with initial PCI. Assessment of the ST-segment dynamics was performed with serial 12-lead ECGs obtained before and after primary PCI within 1-2 hours at 50 mm/sec. In the case of impaired microcirculatory perfusion, the dynamics of ST-segment elevation resolution (STR) remain equal to 70% or less. The real-time myocardial perfusion imaging with myocardial blush grade determination was used to identify no-reflow. ELISA measured the levels of MIF before and after PCI. We found that higher plasma MIF contents were indicated in the entire STEMI patients' population when compared to the healthy volunteers' group (3400 [2089.0-5571.0] pg/mL and 721 [567.3-1104.1] pg/mL respectively, p<0.001), and the pre-PCI MIF contents did not substantially distinguish from post-PCI MIF levels. Patients with no-reflow had significantly higher pre-PCI and post-PCI MIF levels than those who did not have it. ROC characteristics showed that well-balanced cut-off of pre-PCI MIF levels that predicted the no-reflow condition was 3663 pg/mL (sensitivity =74%, specificity =72%, 95% CI=0.585-0.857; p = 0.0023). Pre-PCI MIF levels > 3663 pg/mL predicted the no-reflow, whereas post-PCI MIF levels did not demonstrate a discriminative potency for it. The pre-PCI MIF levels > 3663 pg/mL and female gender were independent predictors for the no-reflow phenomenon. In STEMI patients, elevated pre-PCI MIF levels (>3663 pg/mL and >5033 pg/mL, respectively) predicted post-procedural no-reflow phenomenon and systolic cardiac dysfunction.

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Introduction

Although the implementation of primary Percutaneous Coronary Intervention (PCI) has substantially moved forward the short-run and long-run prognosis and cardiovascular (CV) findings in individuals with ST-segment Elevation Myocardial Infarction (STEMI), peri-procedural events (sudden death, cardiac arrest cardiogenic shock) remain one of the highly important reasons for death among this patient population [1-3]. Several approaches, such as median time shortening from hospital admission to primary PCI, administration of drug-eluting stents, dual antiplatelet therapy, effective lipid-lowering strategy with statins, ezetimibe, and human monoclonal antibodies against proprotein convertase subtilisin / Kexin 9, as well as beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, demonstrated mild-to-moderate benefits in a reduction of in-hospital fatality of STEMI patients with reperfusion damage [4-6]. Moreover, in-hospital management of post-PCI complications is absolutely related to an enhancement in the economic burden on the health system during the last decade worldwide [7].

Ischemia/reperfusion damage of cardiomyocytes and coronary vasculature has resulted in numerous pathological processes, such as downstream embolization by plaque debris, releasing a soluble inflammatory and prothrombogenic factors from the culprit lesion, altered endothelial integrity due to increased vascular permeability and edema of the vascular wall, platelet aggregation, red blood cells and leucocyte adherence, endothelial dysfunction, and vasoconstriction [8-10]. Collectively,

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ultimately structural injury of cardiac myocytes and the vasculature of intramuscular arterioles and walls of capillaries through eventual no-reflow phenomenon, microvascular obstruction, and intramyocardial hemorrhage supports ongoing hypoperfusion of myocardium and leads to adverse cardiac remodeling [11]. In addition, myocardial hypoperfusion following PCI appearing regardless of myocardial infarction size can be predicted and diagnosed by modern biomarker technologies [12, 13].

Macrophage Migration Inhibitory Factor (MIF) is a multifunctional cytokine generated by macrophages and T lymphocytes due to glucocorticoid stimulation and multiple biological properties [14]. MIF is involved in immune reactivity and inflammation, and also it is posed as a crucial factor of the stress response to infection and subsequent tissue damage. MIF level dramatically increased at an early stage of myocardial infarction and probably had predictive value for all-cause mortality and recurrent CV events [15]. MIF levels were positively associated with N-terminal pro-b-type natriuretic peptide (NT-proBNP) contents, adverse cardiac remodeling, and cerebrovascular events among STEMI patients [16, 17]. Therefore, MIF contents in STEMI patients at urgent admission to catheter laboratory correlated with myocardial infarct size estimated with magnetic resonance image [18]. However, it is unclear whether biomarkers of inflammation can predict PCI-related myocardial injury called the no-reflow phenomenon. The study hypothesizes whether circulating MIF levels indicate the reperfusion myocardial injury among STEMI patients.).

Materials and Methods

Patients' Population

Totally 120 patients who presented with a first STEMI and undergone primary PCI were included in the research from an entire cohort of STEMI individuals (n=341). These patients were urgently admitted to the emergency unit of the Government Institution "L. T. Malaya Therapy National Institute NAMSU" and the department of interventional cardiology of the Government Institution "V.T. Zaitsev Institute of General and Emergency Surgery of the NAMS of Ukraine" with STEMI within two to twelve hours of the onset of the first symptoms between October 2019 and December 2020. Twenty-five healthy volunteers were served an age-matched control group. The research design flow chart is reported in **Figure 1**.

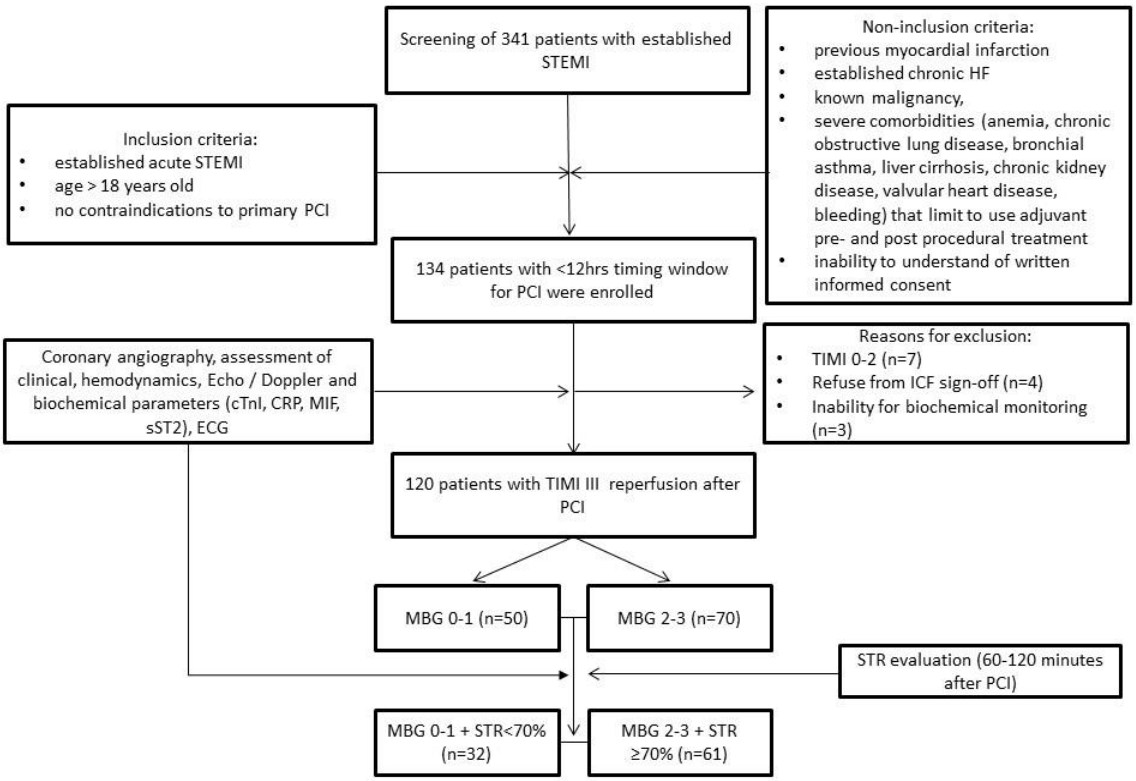


Figure 1. Flow Chart of the Research Design

Abbreviations: CRP, C-reactive protein; cTnI, cardiac troponin I; ECG, electrocardiogram; H.F., heart failure; ICF, informed consent form; MBG, myocardial blush grade; MIF, macrophage migration inhibitory factor; PCI, percutaneous coronary intervention; STEMI, ST-segment Elevation Myocardial Infarction; STR, ST-segment Resolution; sST2, soluble suppression of tumorigenesis 2 protein;- TIMI, Thrombolysis In Myocardial Infarction flow grade.

STEMI, age over 18 years old, and successfully performed primary PCI with epicardial blood flow that corresponded to TIMI III were the inclusion criteria. Patients with severe comorbidities, including active malignancy, chronic inflammatory disease in its acute phase, the presence of known psychiatric disorders - have not been included in the research.

STEMI Determination

STEMI was diagnosed following the ECS Guideline (2017) [19] within the first 12 hours after the onset of the coronary event.

Ethical Declaration

The local Ethics Committee of G.I. "L. T. Malaya Therapy National Institute NAMSU" (Kharkiv, Ukraine) confirmed this study following the Helsinki Declaration (Protocol №5, 26.05.2016). All enrolled patients expressed their agreement in written form for participating in the research.

Coronary Angiography

We used the radial approach by the Seldinger technique to provide conventional coronary angiography. Multiple projections of coronary arteries were recorded for each vessel. Automatic contrast injection of 6-10 mL of the "Ultravist-370" (Bayer Pharma GmbH, Germany) was utilized for contrast enhancement. The radiation exposure fluctuated from 20 to 35 mGycm. Two independent assessors analyzed the contrast images visually and quantitatively. Controversial issues were re-examined by the supervisor (MPK). Unclear angiograms were excluded from further analysis.

Primary PCI

Primary PCI was performed within six to twelve hours after the first symptom onset. Integrity bare-metal stent (Boston Scientific, USA) and Resolute Integrity drug-eluting stent (Medtronic, USA) were implanted in 92 and 42 patients. Adjuvant therapy was provided for all examined patients based on current ESC guidelines.

Assessment of Successful Reperfusion

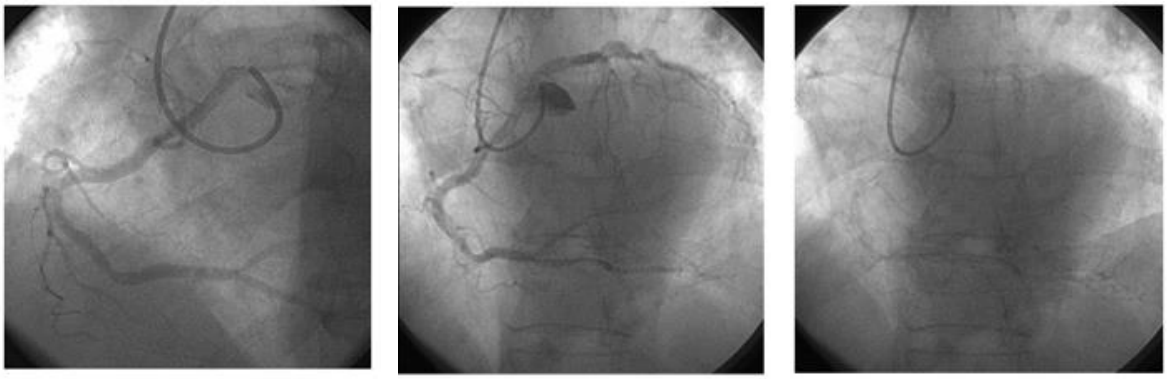
Assessment of the ST-segment dynamics was performed with serial 12-lead ECGs obtained before and after primary PCI within 1-2 hours at 50 mm/sec. In the case of impaired microcirculatory perfusion, the dynamics of ST-segment elevation Resolution (STR) remain equal to 70% and less [20].

STEMI Prognosis Determination

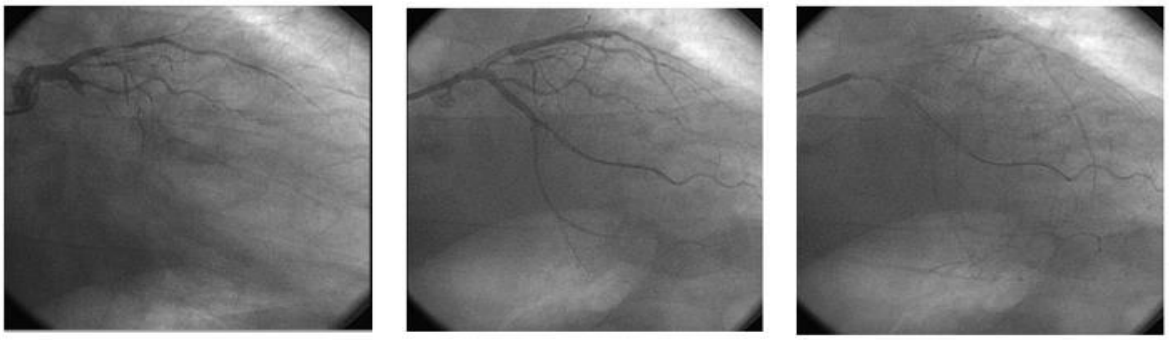
To accredit prognostic capacity after STEMI, we utilized the TIMI and the GRACE score [21, 22].

Real-time Myocardial Perfusion Imaging Determination

The real-time myocardial perfusion imaging with Myocardial Blush determination Grade (MBG) was used to measure myocardial perfusion [23]. The MBG was scored during angiographic analysis according to the conventional method [24]. MBG was graded as 0, 1, 2, and 3 that corresponded to the following criteria: a lack of contrast density of myocardial blush (M.B.), minimal contrast density of M.B., contrast density of M.B. with impaired clearing, and normal M.B. or contrast density, respectively [25]. Occurrence of post-PCI epicardial large coronary artery blood flow of TIMI <3 or MBG 0-1 along with STR <70% within 2 hours after PCI was qualified as the no-reflow condition. **Figure 2** illustrates decision-making performed by the supervisor regarding contrast density and myocardial blush.



a) **b)** **c)**



d) **e)** **f)**

Figure 2. Determination of Contrast Density and Myocardial Blush in STEMI Patients Undergoing Primary PCI **a)** Inferior Infarction with Severe Proximal and Mid RCA Occlusion. **b)** Final Angiographic Image after Stent Implantation with TIMI 3 Flow in RCA. **c)** Lack of Myocardium Staining in the Infarct Area, MBG 0 Grade. **d)** Anterior Infarction with Stenosis of both LAD and LCX. **e)** Final Angiographic Result after Revascularization with TIMI 3 Flow in LAD, as Well as LCX. **f)** MBG 0 Grade Adjusted by Supervisor

Notes: The MBG was based on the visual assessment of contrast density in the infarcted zone of the myocardium and made immediately after PCI by the experienced operator. In the first example, MBG was graded as zero without myocardial blush. During angiographic analysis, the supervisor confirmed MBG 0 grade on recorded angiograms. In the second case, MBG was graded as zero grade with minimal myocardial blush and scored as MBG 0 by the supervisor.
Abbreviations: RCA, right coronary artery; PCI, percutaneous coronary intervention; MBG, Myocardial Blush Grade; LCX, left circumflex artery; LAD, left anterior descending artery; STEMI, ST-segment elevation myocardial infarction

Comorbidities and Risk Factors Determination

Using a questionnaire, the information on disease history, including recent transient ischemic attack and stroke, cancer, hypertension, and medication use (e.g., antihypertensive drugs, lipid-lowering drugs, and hypoglycemic drugs), were evaluated. Trained investigators measured anthropometric factors during the interview. Body Mass Index (BMI) was computed (kg/m2). Dyslipidemia was determined based on the European Society of Cardiology (ESC) dyslipidemia guideline (2019) [26]. The ESC guideline on diagnostics and treatment of arterial hypertension 2018 was used to define hypertensive patients [27]. Based on the ESC guidelines (2016), newly H.F. was diagnosed [28]. Based on the current ADA statement (2017), type 2 diabetes mellitus was detected [29].

Transthoracic Echocardiography and Doppler

Twenty-four hours after admission to the intensive cardiac care unit (ICCU), Transthoracic conventional B-mode echocardiography and Doppler were carried out in all STEMI patients on Toshiba TUS-A500 (Aplio 500, Japan) with 3.5 MHz phase probe with the only operator to minimize bias and left Ventricular End Diastolic Volume (LVEDV), LV End Systolic Volume (LVESV), LV mass (LVM), LV Ejection Fraction (LVEF) based on Simpson's biplane method were measured automatically. Early to late diastolic transmitral flow velocity (E/A) was used to assess diastolic function by impulse Doppler following current recommendation [30].

Calculation of the Sample Size

Through the prospective design of the study, providing the design effect 1.0, confidence intervals of 95%, and the error 5%, the sample size was calculated [31].

Glomerular Filtration Rate Calculation

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used for the calculation of Glomerular Filtration Rate (GFR) [32].

Blood Samples

Blood samples for assay of biomarkers and other routine laboratory analyses were collected at admission before PCI (MIFI, CRPI, sST2), and after PCI according to the following scheme: post-PCI MIF levels were determined in 24 hours after the procedure; the peak levels of cardiac TnI were measured every six hours during 24 hours. Blood specimens were thoroughly centrifuged, isolated within 30 minutes, and frozen in plastic tubes at -70 C until sent to the immunochemical and molecular-genetic research lab of G.I. "L. T. Malaya TNI NAMSU."

Determination of serum biomarkers was performed by enzyme-linked immunosorbent assay using commercial kits. MIF contents were evaluated by Humalyzer 2000 (HUMAN GmbH, Germany) using a «Human MIF ELISA» (RayBio, USA) kit with the upper reference limits 6000.0 pg/ml. sST2 contents were evaluated by «The Presage ST2 Assay» (Critical Diagnostics, CA, USA) kit with the limits of 0 - 200.0 ng/ml according to the manufacturers' recommendations. The levels

of troponin I (TnI) and C-reactive protein (CRP) were determined by «Troponin I-ELISA» (Xema, Russia) kit with the limits of 0-10.0 ng/ml and «CRP-ELISA» (Xema, Russia) kit with the upper limit of 25.0 mg/L, respectively.

Direct enzymatic method (Roche P800 analyzer, Basel, Switzerland) was used to measure Total Cholesterol (T.C.), High-density Lipoprotein (HDL) Cholesterol, Low-density Lipoprotein (LDL) Cholesterol, and Triglycerides (T.G.). The inter-and intra-assay coefficients of variation were <5%.

Fasting glucose level was evaluated by double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany).

Statistics

We used the "Statistica" v. 10.0 (Stat Soft Inc, Tulsa, OK, USA) to perform statistical analysis. Continuous and categorical variables were expressed as means (S.D.s) and as counts (percentages), respectively. Suppose distributed normally or expressed as medians (interquartile ranges [IQR]) if data presented a skewed distribution. The Shapiro-Wilk test was used to test data distribution. Continuous variables were compared with Student's t-test, one-way ANOVA, or non-parametric tests (Mann-Whitney or Kruskal-Wallis test) between groups. Categorical variables were compared with the chi-square test. Correlations between variables were performed using the Spearman test. The Receiver Operational Characteristic (ROC) curve analysis was carried out to detect a well-balanced cut-off of biomarker concentration. Area Under Curve (AUC), specificity, and sensitivity were calculated for cut-off point, determined by the Youden method [33]. Logistic regression was used to analyze the association of multiple factors with myocardial perfusion disturbance. Odds Ratio (OR), β-coefficient, 95% Confidence Interval (CI) were calculated for each factor contributing to the no-reflow phenomenon. P-value less than or equal to 0.05 was considered statistically significant.

Results and Discussion

The baseline clinical specifications of patients who were involved in the research are presented in **Table 1**. The entire patients' population exists mainly of males (70.9%) having a wide range of CV risk factors including hypertension (78.4%), type 2 diabetes mellitus (33.6%), smoking (45.8%), mild-to-moderate obesity (42.5%) with a family background of coronary artery disease (44.8%).

Table 1. Baseline Specifications of the Research Patients

	Entire STEMI patients' cohort (n=134)	Patients with post-PCI no-reflow condition (MBG 0-1, STR<70%, n=32)	Patients without post-PCI no-reflow condition (MBG 2-3, STR>70%, n=61)	P value
Clinical data, previous medical history				
Age, years	61.36±10.43	65.31±10.03	62.25±9.67	0.066*
Male, n (%)	95 (70.9)	23 (71.9)	41 (67.2)	0.645
Female, n (%)	39 (29.1)	9 (28.1)	20 (32.8)	
Systolic blood pressure, mm Hg	133.90±30.51	125.22±34.85	139.05±26.49	0.110
Diastolic blood pressure, mm Hg	80.12±14.97	76.66±15.43	81.93±15.41	0.321
Heart rate, beats/min	79.22±16.74	84.38±23.29	77.18±15.41	0.104
Hypertension, n (%)	105 (78.4)	28 (87.5)	48 (78.7)	0.226
Type 2 diabetes mellitus, n (%)	45 (33.6)	12 (37.5)	17 (27.9)	0.341
Smoking, n (%)	65 (48.5)	12 (37.5)	28 (45.9)	0.437
BMI>30 kg/m^2, n (%)	57 (42.5)	6 (18.8)	13 (21.3)	0.771
Stable angina before STEMI, n (%)	63 (47.0)	18 (56.3)	30 (49.2)	0.517
Unstable angina before STEMI, n (%)	24 (17.9)	9 (28.1)	8 (13.1)	0.134
Family history of CAD, n (%)	60 (44.8)	12 (37.5)	31 (50.8)	0.221
Echocardiographic parameters				
LVEDV, mL	126.03±30.35	131.59±15.01	125.74±28.42	0.663
LVEDV index, mL/m^2	64.35±15.03	68.31±16.36	65.21±14.50	0.440
LVESV, mL	60.84±22.26	65.73±24.27	62.32±21.07	0.690
LVM, g	221.29±77.88	227.09±60.34	209.22±76.75	0.266
LVM index, g/m^2	109.41±41.42	118.04±30.96	103.21±41.64	0.144
LVEF, %	49.72±8.66	45.00±6.95	49.79±7.81	0.018*
E/A	1.08±0.38	0.99±0.44	1.09±0.33	0.221
STEMI risk scores				
GRACE risk score (in-hospital), points	140.38±35.31	162.00±48.67	138.05±27.74	0.023*

GRACE risk score (admission - 6-month), points	115.83±30.73	135.72±39.30	114.27±24.83	0.009*
TIMI risk score, points	3.82±2.40	5.25±2.63	3.44±2.14	0.001*
STEMI localization				
Anterior, n (%)	64 (47.8)	23 (71.9)	24 (39.3)	0.006*
Posterior, n (%)	70 (52.2)	9 (28.1)	37 (60.7)	0.003
LMCA, n (%)	10 (7.5)	2 (5.4)	4 (6,6)	0.662
LAD, n (%)	94 (70.1)	27 (84.4)	38 (62.3)	0.022*
RCA, n (%)	85 (63.4)	18 (56.3)	39 (63.9)	0.588
LCX, n (%)	47 (35.1)	17 (53.1)	21 (34.4)	0.081
The number of injured coronary vessels				
One-vessel injury, n (%)	55 (41.0)	12 (37.5)	26 (42.6)	0.633
Two-vessel injury, n (%)	40 (29.9)	8 (25.0)	20 (32.8)	0.437
Three and multiple vessel injury, n (%)	39 (29.1)	12 (37.5)	15 (24.6)	0.193
Biomarkers				
Peak TnI, ng/mL	9.06±4.27	10.74±3.45	9.01±4.21	0.106
MIF_I, pg/mL	2501.0 [1409.0-3896.5]	3262.0 [2260.5-5951.5]	2261.0 [1324-3400]	0.004
MIF_{II}, pg/mL	2395.5 [1252.0-4140.5]	3287.0 [1927.0-4303]	2008.5 [1202.0-3507.0]	0.015
sST2, ng/mL	24.36 [17.59-30.38]	42.1 [30.69-135.74]	33.08 [20.15-56.6]	0.045
CRP_I mg/L	18.90±9.53	19.02±9.77	19.24±9.53	0.863
CRP_{II} mg/L	23.23±8.80	23.37±9.55	22.64±8.32	0.763
Serum creatinine, μmol/L	104.01±29.46	109.99±32.49	104.96±31.84	0.363
GFR (CKD-EPI), ml/min/1.73m^2	66.22±20.23	62.52±22.26	64.36±18.99	0.685
Blood glucose, mmol/L	9.59±4.78	10.74±5.67	8.78±4.30	0.171
Hemoglobin, g/L	140.02±16.60	138.13±15.01	139.23±17.50	0.937
WBC, 10^9/L	10.44±3.80	12.24±3.96	10.36±3.74	0.025
TC, mmol/L	5.03±1.33	4.53±1.41	5.39±1.33	0.007
LDL, mmol/L	3.13±1.25	2.82±1.27	3.35±1.31	0.062
HDL, mmol/L	1.05±0.34	1.01±0.26	1.06±0.35	0.948
TG, mmol/L	1.87±1.12	1.55±0.69	2.06±1.43	0.044
In-hospital complications				
Total number of in-hospital complications (acute heart failure, cardiac aneurysm, newly atrial fibrillation / flatter and sustainable ventricular tachycardia), n (%)	29 (21.6)	15 (46.9)	9 (14.8)	0.002
II-III Killip class of HF, n (%)	18 (13.4)	7 (21.9)	7 (11.5)	0.304
IV Killip class of HF, n (%)	10 (7.5)	6 (18.6)	3 (4.9)	0.041
Out-hospital complications				
Combined endpoints, n (%)	43 (32.1)	17 (53.1)	16 (26.2)	0.010
Concomitant medication				
Aspirin, n (%)	134 (100)	32 (100)	61 (100)	1.0
Clopidogrel, n (%)	44 (32.8)	12 (37.5)	22 (36.1)	0.892
Ticagrelor, n (%)	89 (66.4)	19 (59.4)	39 (63.9)	0.666
Statins, n (%)	134 (100)	32 (100)	61 (100)	1.0
β-blockers, n (%)	119 (88.8)	28 (87.5)	53 (86.8)	0.94
ACEI/ARBs	112 (83.5)	30 (93.7)	55 (90.1)	0.96
MRA	8 (6.0)	3 (9.4)	3 (4.9)	0.338

Abbreviations: CAD, chronic stable angina pectoris, ARBs, Angiotensin II Receptor Blockers; ACEI, Angiotensin-converting-enzyme Inhibitors; CRP, C-reactive Protein; BMI, Body Mass Index; GFR, glomerular filtration rate; E/A, early to late diastolic transmitral flow velocity; HDL, High-density Lipoprotein; H.F., heart failure; LAD, Left Anterior Descending artery; LDL, Low-density Lipoprotein; LCX, left circumflex artery; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; LVESV, Left Ventricular End Systolic Volume; LVM, Left Ventricular Mass; LVPWs, Left Ventricle Posterior Wall Thickness; MIF, macrophage Migration Inhibitory Factor; LMCA, Left Main Coronary Artery; RCA, Right Coronary Artery; STEMI, ST-segment Elevation Myocardial Infarction; sST2, Soluble Suppression of Tumorigenesis 2 Protein; T.C., Total Cholesterol; T.G., Triglycerides; TnI, Troponin I; MRA, Mineralocorticoid Receptor Antagonists.

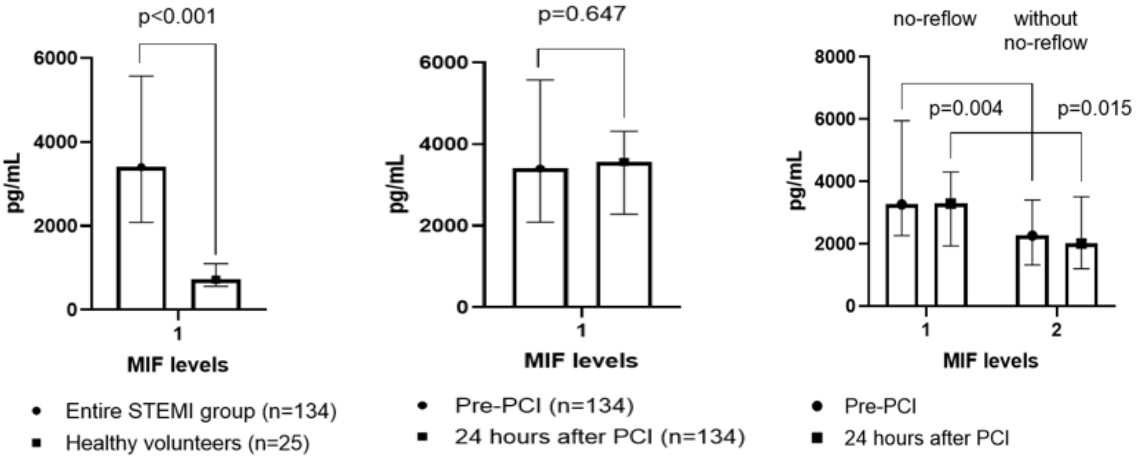
These individuals did not have severe left ventricular (LV) dilatation, while the mean LV ejection fraction was 49.7% (95% interquartile range was from 40.2% to 49.5%). The majority of them had posterior localization of STEMI, mild-to-moderate

risk according to GRACE and TIMI risk scores, and finally, almost 60% demonstrated two-vessel and multiple vessel injury. Therefore, about 22% of STEMI patients from the entire population met in-hospital complications (acute heart failure, cardiac aneurysm, newly atrial fibrillation/flutter, and sustainable ventricular tachycardia). The concomitant medications included antiplatelets, beta-blockers, statins, mineralocorticoid receptors, ACE inhibitors/angiotensin-II receptor antagonists, and antagonists.

STEMI patients with post-PCI no-reflow condition (MBG 0-1, STR<70%) had lower LV ejection fraction (p=0.018) and higher levels of sST2 (p=0.045), TC (p=0.025), TG (p=0.007), white blood cells (p=0.044) than those who did not have this phenomenon. In addition, anterior STEMI localization (p=0.006) along with a lesion of the left anterior descending artery (p=0.022) were found to have prevailed in individuals with the post-PCI no-reflow condition when compared with patients without it. No substantial differences were found between cohorts in the levels of other biomarkers, including creatinine, TnI, C-reactive protein, and concomitant medications.

Determination of MIF Levels in STEMI Patients

Figure 3 illustrates the levels of MIF in STEMI patients in comparison with healthy volunteers and a difference between STEMI cohorts in this biomarker. Higher plasma MIF levels were indicated in entire STEMI patients' population when compared to healthy volunteers' group (3400 [2089.0-5571.0] pg/mL and 721 [567.3-1104.1] pg/mL respectively, p<0.001) **(Figure 3a)**. **Figure 3b** shows the pre-PCI MIF levels did not substantially distinguish from post-PCI MIF levels measured 24 hours after the procedure (3400 [2089.0-5571.0] pg/mL, and 3563 [2283.0-4311.0] pg/mL, respectively, p=0.647). Nevertheless, patients with no-reflow condition had significantly higher pre-PCI and post-PCI MIF levels than those who did not demonstrated no-reflow phenomenon (3262.0 [2260.5-5951.5] pg/mL and 2261.0 [1324-3400] pg/mL respectively, p=0.004, respectively, and 3287.0 [1927.0-4303] pg/mL and 2008.5 [1202.0-3507.0] pg/mL respectively, p=0.015, respectively) **(Figure 3c)**.



a) **b)** **c)**

Figure 3. The Levels of MIF in STEMI Patients and Healthy Volunteers

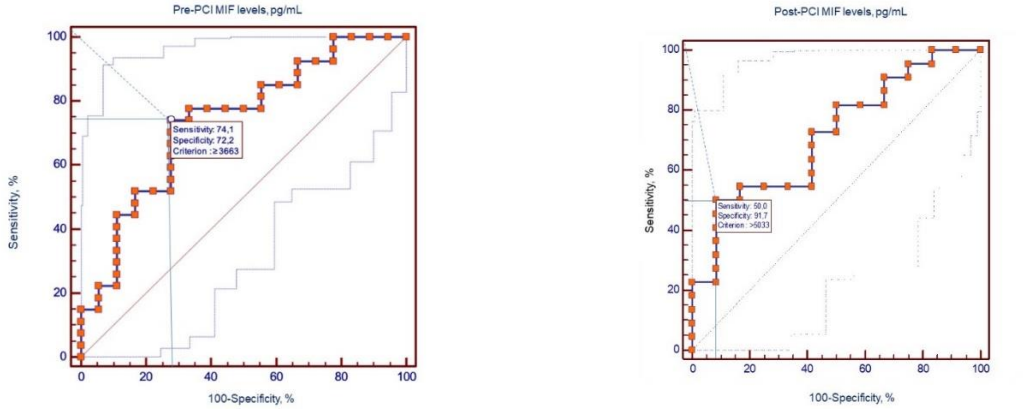
a) The Comparison of the MIF Levels in Entire STEMI Patients' Population and Healthy Volunteers' Group. **b)** The Comparison of Pre-and Post PCI MIF Levels in Entire STEMI Patients' Population. **c)** The Comparison of Pre-and Post PCI MIF Levels in STEMI Cohorts

Spearman Correlations between MIF Levels, other Circulating Biomarkers, Cardiac Hemodynamics' Parameters, Risk Factors and Comorbidities

Spearman's rank correlation test revealed that there were positive relationships between MIF contents and LV mass index (r=0.75; p=0.007), LVEDV (p=0.001), LVESV (p=0.02), peak TnI levels (r=0.44; p=0.002), white blood cells count (r=0.33, p=0.0001), C-reactive protein (r=0.19, p=0.032), but not with sST2 levels, T2DM, and GRACE score. Pre-PCI levels of sST2 positively correlated with GRACE score (r=0.42; p=0.001), T2DM (r=0.41; p=0.001), acute heart failure Killip class (r=0.40; p=0.001), age (r=-0.36; P=0.001), peak TnI levels (r=0,33; p=0,001), and inversely correlated with LV ejection fraction (r=-0.40; p=0.001), LDLP cholesterol (r=-0.33; p=0.007). Pre-PCI LV ejection fraction was associated with GRACE risk score (r=-0.40; p=0.001), T2DM (r=0.38; p=0.001), age (r=0.32; p=0.002), male gender (r=0.31; p=0.001), a number of culprit coronary arteries (r=-0.31; p=0.002), and peak TnI (r=0.38; p=0.003).

MIF as Predictor for No-reflow Condition: Receive Operation Curve Analysis

Using the ROC analysis, we concluded that well-balanced cut-off of pre-PCI MIF levels that predicted the no-reflow condition was 3663 pg/mL (sensitivity =74%, specificity =72%, AUC= 0.74; 95% CI=0.585-0.857; p = 0.0023) **(Figure 4a)**. Post-PCI MIF level cut-off point was determined 2380 pg/mL (sensitivity = 48%, specificity =89%, AUC= 0.65; 95% CI=0.500 to 0.791; p =0.07) **(Figure 4b)**.



a) **b)**

Figure 4. Predictive Value of Circulating Pre-PCI MIF Levels for No-reflow Phenomenon in STEMI Patients: The ROC Analysis

a) Predictive Value of Pre-PCI MIF Levels. **b)** Predictive Value of Post-PCI MIF Levels

MIF Levels as Predictor for Reduced Left Ventricular Ejection Fraction: Receive Operation Curve analysis

ROC analysis has indicated that pre-PCI MIF contents >5033 pg/mL independently anticipated LV systolic dysfunction that was determined as reduced (<40%) LV ejection fraction (sensitivity=50.0%; specificity=91.7%, AUC=0.716; 95% CI=0.536 to 0.857, p=0.0189) **(Figure 5)**, whether post-PCI MIF levels did not.

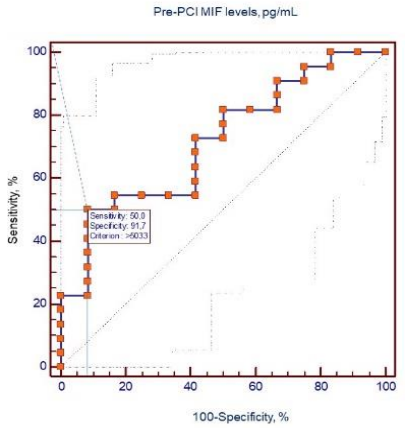


Figure 5. MIF Levels as Predictor for Reduced Left Ventricular Ejection Fraction: Receive Operation Curve analysis

Predictive Factors for Post-PCI No-reflow Phenomenon: The Results of Univariate and Multivariate Regressions

Using univariate and multivariate regressions, we identified the factors related to the post-PCI no-reflow phenomenon in STEMI patients **(Table 2)**.

Table 2. The Factors Related with Post-PCI No-reflow Phenomenon in STEMI Patients: Univariate and Multivariate regressions

Variables	Univariate analysis				Multivariate analysis			
	β- coefficient	OR	95% CI	p-value	β- coefficient	OR	95% CI	p-value
Age	-1.1	0.3	0.0-29.3	0.627		-		
Gender (female)	15.1	3.9	0.0-5.3	0.684	2.8	17.7	0.9-327.2	0.053
Smoking	2.7	15.6	0.0-31.7	0.658		-		
T2DM	-51.6	0.0	-	0.982		-		
Number of culprit vessels	-10.6	0.0	0.0-0.0	0.697		-		
STEMI localization	-16.0	0.0	0.0-0.0	0.649		-		
CRP	0.6	1.8	0.2-12.0	0.521		-		
Pre-PCI MIF > 3663 pg/mL	0.0033	1.0	0.9-1.0	0.664	0.1	1.1	1.0-1.2	0.036
Post-PCI MIF >2380 pg/mL	-0.001	0.9	0.9-1.0	0.779		-		

sST2	-0.2	0.8	0.3-1.9	0.631	-
Peak TnI level	-0.1	0.8	0.0- 9.7	0.894	-

Abbreviations: MIF, Macrophage Migration Inhibitory Factor; CRP, C-reactive Protein; OR, Odds Ratio; sST2, Soluble Suppression of Tumorigenesis 2 Protein; CI, Confidential Interval; TnI, Troponin I; T2DM, Type 2 Diabetes Mellitus

Pre-PCI MIF levels > 3663 pg/mL and female gender were independent predictors for no-reflow phenomenon (β-coefficient 0.1; OR 1.1; 95% CI 1.0-1.2; p=0.036 and β-coefficient 2.9; OR 17.7; 95% CI 0.9-327.2; p=0.053, respectively).

The research findings unveiled the predictive capability of pre-PCI MIF levels for no-reflow phenomenon and declining post-PCI left ventricular pump function. No-reflow is traditionally defined as a PCI–related myocardial hypoperfusion in STEMI patients, closely associated with poor clinical outcomes (increased mortality rate and recurrent short-term hospitalization), adverse cardiac remodeling, and heart failure development [34, 35]. Because MIF promotes inflammatory response by inducing several inflammatory cytokines and shaping NLRP3 inflammasomes releasing from circulating leukocytes, early-rised levels of these inflammatory cytokines in STEMI patients are considered a powerful indicator of advanced oxidative stress recurrent ischemia-reperfusion injury of myocardium and vasculature [36, 37]. On the other hand, MIF induces reparative angiogenesis/neovascularization, cardiomyocyte survival, and endothelial progenitor cell differentiation/proliferation and prevents apoptosis of cardiac myocytes and endothelial cell precursors [38]. In this context, MIF may be discussed as an adaptive multifunctional cytokine with cardiac and vessels' protective capacity and promotion for collateral development, peak levels of which remarkably reflect adaptive response against the severity of microvascular inflammation, endothelial dysfunction, cardiac dysfunction, and remodeling, anticipate poor clinical results in STEMI patients [16, 39].

Although several clinical studies have been reported that MIF levels were negatively related to the left ventricular ejection fraction depending on the presence of T2DM and other CV comorbidities [39, 40], in this study, we did not find clear confirmation for these previous issues. The pre-PCI levels of MIF correlated with peak troponin level, the GRACE score, LV systolic and diastolic dimensions, and LV ejection fraction. These findings corresponded to the results obtained by other investigators [41, 42]. In addition, we found that pre-PCI MIF levels >3663 pg/mL predicted post-procedural no-reflow phenomenon and that elevated pre-PCI concentrations of MIF>5033 pg/mL had a high discriminative capacity for impaired LV systolic function after PCI. Interestingly, post-PCI MIF levels demonstrated a weak ability to predict no-reflow and did not show strong discriminative potency for left ventricular systolic dysfunction. Yet, elevated levels of other biomarkers, such as TnI, CRP, and sST2, did not yield their prognostic values to predict the no-reflow whatsoever. Indeed, Zhao Q *et al*. (2019) [43] reported that MIF levels at admission being elevated in the majority of individuals with STEMI treated with PCI predicted in-hospital CV mortality and Major Adverse Cardio-and/or Cerebrovascular Events (MACCE) during a period of hospitalization and in long-term follow-up. In contrast, conventional biomarkers had no demonstrated strong evidence for post-PCI complications. However, there is evidence that pre-PCI sST2 was able to predict no-reflow in STEMI [44, 45]. Because sST2 concentrations in STEMI patients on admission were well positively related with the degree of large coronary artery stenosis, we suggested that sST2 and MIF can predict both no-reflow and MACCE in PCI treated STEMI patients in different ways. SST2, being strongly associated with multivessel large coronary disease, independently predicts reperfusion damage along with microvascular inflammation, whereas MIF might reflect ischemia-induced preconditioning condition in CAD patients. However, the findings of the previously reported meta-analysis of 27 retrospective and prospective studies on PCI-induced myocardial dysfunction unveiled that the primary TIMI flow ≤1 and high thrombus burden exhibited a dramatic effect on the survival of STEMI patients [46]. Consequently, delayed complete reperfusion of ischemic stenosis could be a powerful co-factor interfering with the predictive ability of inflammatory biomarkers on no-reflow after successful PCI.

MIF playing an essential role in ischemic preconditioning-induced myocardial protection may ameliorate altered cardiac function and adverse cardiac remodeling through various ways, including suppression of ischemia-induced salvage kinase pathway, CD74/ AMP-activated protein kinase signal system, and its components [47, 48]. In addition, MIF exerts protective effects by suppression of myocardial healing and maintenance of cardiac function through promoting CXCR2 in resident cells [49]. Eventually, MIF can down-regulate the level of apoptosis of injured cardiac myocytes and circulating mature and progenitor endothelial cells, thereby preventing them from revascularization damage [49]. However, these data allow us to explain the plausible molecular mechanisms by which pre-PCI MIF influenced coronary blood flow recovery and myocardial function maintenance.

Notably, in our study, the female gender was found a risk factor for no-reflow after primary PCI along with pre-PCI MIF. Although previous investigations have yielded conflicting results regarding short-term, not long-term, mortality rate and adverse clinical outcomes among women after primary PTCA for STEMI, it has been suggested that a signature of comorbidities, such as type two diabetes mellitus, chronic kidney disease, and hypertension would be a crucial element to thoroughly describe the role of female gender in prognosis after STEMI [50]. We hypothesized that pre-PCI levels of circulating MIF being regulated by sex hormones and white adipose tissue-related cytokines, which might exert variable impact on reperfusion damage. Indeed, sex and sex hormones influencing surrogate inflammatory markers and ectopic fat deposition could mediate the protective role of MIF [50]. However, this assumption requires more deep investigation in a large clinical study in the future.

Study Limitations

The research had several limitations. The first limitation was a small size, while the study's methodology allowed us to analyze the discriminative value of MIF levels for post-PCI no-reflow. The cardiac magnetic resonance imaging was not carried out to evaluate the infarct or microvascular obstruction. However, after PCI, we evaluated a peak value of troponin, angiographic TIMI, MBG, and ST-segment resolution. Moreover, except for CRP, we did not analyze additional biomarkers of inflammation that might link the increasing of MIF to inflammatory reactions. Yet, the study was conducted in a single-center, and a selection bias could have existed. However, we believe that the study limitations would not have a sufficient impact on the research findings.

Conclusion

Our study results reveal that an early increase of MIF levels in STEMI may be predictive for no-reflow after primary successful PCI.

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Conflict of interest: None

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Ethics statement: This study was approved by the local Ethics Committee of G.I. "L. T. Malaya TNI NAMSU" (Kharkiv, Ukraine) following the Helsinki Declaration (Protocol №5, 26.05.2016). All enrolled patients gave their informed written consent to participate in the study.

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